



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

AB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,217	02/21/2002	Gregory R. Mundy	A061CIP2	5114
26161	7590	11/16/2004	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			HADDAD, MAHER M	
			ART UNIT	PAPER NUMBER

1644

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/086,217	<b>Applicant(s)</b> MUNDY ET AL.	
	<b>Examiner</b> Maher M. Haddad	<b>Art Unit</b> 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 08 October 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 86-101 is/are pending in the application.
- 4a) Of the above claim(s) 90 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 86-89 and 91-101 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/20/03, 7/5/02, 4-6/21/02</u> | 6) <input type="checkbox"/> Other: _____  |

Art Unit: 1644

#### DETAILED ACTION

1. Claims 86-101 are pending.
2. Applicant's election of Group II, claims 1, 51 and 53-61, (now claims 86-89 and 91-101) drawn to a method of treating multiple myeloma with a composition comprising an antagonist, wherein the antagonist is an antagonist of VLA-4 and the species of chemotherapeutic agent melphalan in the reply filed on 10/08/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
3. Claim 90 (non-elected species) is withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.
4. Claims 86-89 and 91-101 are under examination as they read on a method of treating multiple myeloma with a composition comprising an anti-VLA-4 antibody or antibody homolog and the species of chemotherapeutic agent melphalan.
5. Applicant's IDS, filed 10/20/03, 7/05/02 and 6/21/02, is acknowledged, however, Michigami et al reference filed on 7/5/02 is crossed out as it is a duplicate of the Michigami et al reference filed on 6/21/02.
6. The following is a quotation of the second paragraph of 35 U.S.C. 112.  
*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*
7. Claims 93-95 and 98-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
  1. Claims 93-95 are indefinite in the recitation "than not administered in combination with said second composition. Claims 93-95 depend from claims 87-90 which claim the combination of both antagonist and a second composition, it is unclear how the antagonist would be administered in the absent of the second composition since the base claims require a combination therapy.
  2. Claims 98-100 are indefinite in the recitation of "21.6" because its characteristics are not known. The use of "21.6" antibody homology as the sole means of identifying the claimed antibody renders the claim indefinite because "21.6" are merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct antibody.

Art Unit: 1644

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

8. Claims 86-89 and 91-101 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

It appears that the "21.6" antibodies are essential to practice the claimed invention. However the specification fails to teach how to make the specific antibodies. Applicant's attempt to incorporate "21.6" by reference to PCT/US95/01219 is considered improper.

The incorporation of essential material in the specification by reference to PCT/US95/01219 (page 43) for "21.6" is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to "21.6" is improper because an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, see MPEP 608.01(p). "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See *In re Fouche*, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Further, It is apparent that the antibody "21.6" are essential and required to practice the claimed invention. As a required element, the hybridoma that secret the "21.6" must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

Art Unit: 1644

If the deposits have been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposits were made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

Further, besides the method of treating multiple myeloma comprising an anti-VLA-4 antibody and melphalan, does not reasonably provide enablement for any method for treating multiple myeloma comprising administering to the subject a combination of an anti-VLA-4 antibody or "antibody homolog" and any chemotherapeutic agent in claim 86, wherein the combination comprises a therapeutically or prophylactically effective amount of a first composition comprising the anti-VLA-4 antibody or antibody homolog and a therapeutically or prophylactically effective amount of a first composition comprising the anti-VLA-4 antibody or "antibody homolog" and a therapeutically or prophylactically effective amount of a second composition comprising the "chemotherapeutic agent" in claim 87, wherein the antibody or antibody homolog is a monoclonal antibody or "monoclonal antibody homolog" in claim 91, wherein an anti-VLA-4 antibody homolog is "a human antibody homolog, a chimeric antibody homolog, a humanized antibody homolog, and a Fab, Fab', F(ab')<sub>2</sub> or F(v) fragment thereof", is administered in claim 92, wherein the anti-VLA-4 or antibody homolog is a "B epitope specific" anti-VLA-4 antibody or antibody homolog in claim 67, wherein the administering step comprises administering an anti-VLA-4 antibody homolog comprising a humanized light chain and a humanized heavy chain, the light chain and the heavy chain each comprising CDR1, CDR2 and CDR3 from a

Art Unit: 1644

“murin 21.6 anti-VLA-4 antibody” in claim 98, wherein “at least one amino acid position of the framework region is occupied by the amino acid present in the equivalent position of the murine 21.6 immunoglobulin “ in claim 99 or a method for treating MM in a subject comprising administering to the subject a combination of (i) an anti-VLA-4 antibody homolog comprising a humanized light chain and a humanized heavy chain the light chain and the heavy chain each comprising CDRs from a murine 21.6 anti-VLA-4 antibody, and (ii) melphalan in claim 100 or a method for treating multiple myeloma in a subject comprising administering to the subject a combination of (i) anti-VLA-4 antibody or antibody homolog, wherein the antibody or antibody homolog is a B epitope specific anti-VLA-4 antibody or antibody homolog and (ii) melphalan in claim 101 wherein said combination is therapeutically or “prophylactically” effective to treat MM in the subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention.

Besides, the anti-VLA-4 antibody, the specification does not provide sufficient guidance and direction as how to make and use any “antibody homolog” of anti-VLA-4 and any therapeutic agent”, wherein the combination would lead to therapeutically or prophylactically effective to treat multiple myeloma in the subject, wherein the antibody is a “B epitope specific anti-VLA – 4”.

While the specification on page 37, line 4-12 discloses that B epitope-specific antibodies as antibodies which can bind to VLA-4 at a site involved in ligand recognition and block VCAM-1 and fibronectin binding, however, the specification lacks guidance of the structure or what part of the VLA-4 involved in the ligand recognition and block VCAM-1 and fibronectin binding. The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only the antibodies against  $\alpha 4$  and a melphalan, a bisphosphonate, thalidomide and erythropoietin as chemotherapeutic agent. A person of skill in the art is not enabled to make and use “an antagonist” and “a compound” as recited in claims. A person of skill in the art would not know which antagonists or compounds are essential to treat MM. Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies such “B epitope” for  $\alpha 4$ .

Further, while the specification on page 32 lines 23-30 discloses that the term “antibody homolog” includes intact antibodies consisting of immunoglobulin light and heavy chains linked via disulfide bonds. The term “antibody homolog” is also intended to encompass a protein comprising one or more polypeptides selected from immunoglobulin light chains polypeptides selected from immunoglobulin light chains, immunoglobulin heavy chains and antigen-binding fragments thereof which are capable of binding to one or more antigens. The component polypeptides of an antibody homolog composed of more than one polypeptide may optionally be disulfide-bound or otherwise covalently crosslinked. However, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of

Art Unit: 1644

three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibody homolog as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an anti-VLA-4 antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce antibody homolog and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional humanize antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (US Patent 6,632,927) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (col.2 lines 58-61). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity.

In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Further, at issue whether the claimed combination of the anti-VLA-4 and the therapeutic agent would lead to prophylactic results in MM. However, an effective protocol for the prevention MM in a subject is subject to a number of factors which enter the picture beyond simply the administration of the therapeutic composition in an acceptable formulation. Demonstrating inhibition of VLA-4 dependent firm adherence cannot alone support the predictability of the method for preventing said MM through administration of the appropriate formulation. The ability of a host to suppress and thereby prevent MM will vary depending upon factors such as the condition of the host and burden of disease.

The specification does not provide sufficient teaching as to how it can be assessed that preventing MM in the assay was achieved after the administration of the therapeutic composition of the invention. Further, the specification does not provide sufficient teachings as what is the target population that needs the prevention treatment.

Art Unit: 1644

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 86-89 and 91-101 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of treating multiple myeloma comprising an anti-VLA-4 antibody and melphalan.

Applicant is not in possession of any method for treating multiple myeloma comprising administering to the subject a combination of an anti-VLA-4 antibody or "antibody homolog" and any chemotherapeutic agent in claim 86, wherein the combination comprises a therapeutically or prophylactically effective amount of a first composition comprising the anti-VLA-4 antibody or antibody homolog and a therapeutically or prophylactically effective amount of a first composition comprising the anti-VLA-4 antibody or "antibody homolog" and a therapeutically or prophylactically effective amount of a second composition comprising the "chemotherapeutic agent" in claim 87, wherein the antibody or antibody homolog is a monoclonal antibody or "monoclonal antibody homolog" in claim 91, wherein an anti-VLA-4 antibody homolog is "a human antibody homolog, a chimeric antibody homolog, a humanized antibody homolog, and a Fab, Fab', F(ab')<sub>2</sub> or F(v) fragment thereof", is administered in claim 92, wherein the anti-VLA-4 or antibody homolog is a "B epitope specific" anti-VLA-4 antibody or antibody homolog in claim 67, , wherein the administering step comprises administering an anti-VLA-4 antibody homolog comprising a humanized light chain and a humanized heavy chain, the light chain and the heavy chain each comprising CDR1, CDR2 and CDR3 from a "murin 21.6 anti-VLA-4 antibody" in claim 98, wherein "at least one amino acid position of the framework region is occupied by the amino acid present in the equivalent position of the murine 21.6 immunoglobulin " in claim 99 or a method for treating MM in a subject comprising administering to the subject a combination of (i) an anti-VLA-4 antibody homolog comprising a humanized light chain and a humanized heavy chain the light chain and the heavy chain each comprising CDRs from a murine 21.6 anti-VLA-4 antibody, and (ii) melphalan in claim 100 or a method for treating multiple myeloma in a subject comprising administering to the subject a combination of (i) anti-VLA-4 antibody or antibody homolog, wherein the antibody or antibody homolog is a B epitope specific anti-VLA-4 antibody or antibody homolog and (ii) melphalan in claim 101 wherein said combination is therapeutically or "prophylactically" effective to treat MM in the subject.



Art Unit: 1644

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (antibody homolog) to describe the claimed genus, nor does it provide a description of structural features that are common to species (B epitope). The specification provides no structural description of B epitopes or antibody homolog other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed B epitope and the antibody homolog looks like. The specification's disclosure is inadequate to describe the claimed genus of antibody homolog.

Applicant has disclosed only anti- $\alpha$ 4 antibodies and melphalan, a bisphosphonate, thalidomide and erythropoietin; therefore, the skilled artisan cannot envision all the contemplated antagonist, agent and compound possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3<sup>rd</sup> column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The filing date of the instant claims is deemed to be 08/31/2001, as the parent application is drawn only to the administration of anti- $\alpha$ 4 antibody, and thus does not support the claimed limitations of the instant application of a combined administration of melphalan and anti- $\alpha$ 4 antibody. Further, the filing date for the limitation B epitope is deemed to be the filing date of the instant application (i.e., 02/21/2002).

Art Unit: 1644

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 86-89, 91, 93-97 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. A1 and Lokhorst et al (Blood 84:2269-2277, 1994) and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969).

Van Zaanen et al teach a method for treating multiple myeloma comprising administering chimaeric monoclonal anti-IL-6 antibodies (cMab) in multiple myeloma patients, the cMab was given in a dosage of 5-40 mg/d (see the entire document and the abstract on page 783 in particular).

The Van Zaanen *et al* teaching differs from the claimed invention by not expressly disclosing to employ a combination of an anti-VLA-4 antibody or antibody homolog and a chemotherapeutic agent in claim 86, wherein wherein the chemotherapeutic agent is melphalan in claims 88-89, wherein the anti-VLA-4 antibody or antibody homolog binds the alpha chain of VLA-4 in claim 96, wherein the anti-VLA-4 antibody or antibody homolog is a B epitope specific anti-VLA-4 antibody or antibody homolog in claim 97, wherein to be therapeutically effective, a dosage of said antiagonist is lower when administered in combination with said second composition than not administered in combination with said second composition; or a dosage of said compound is lower when administered in combination with said first composition than not administered in combination with said second composition, or both in claims 93-95

Masellis-Smith *et al* teach function-blocking monoclonal antibodies such as mAbs against very late antigen 4 that inhibit the CD19+ multiple myelom blood B cell interaction with BM fibroblasts. Furthermore, Masellis-Smith *et al* teach that the alpha4beta7 ligand is mediated MM blood B cell adhesion (see the entire document and abstract page 930 in particular).

Art Unit: 1644

Lokhorst *et al* teach monoclonal antibodies directed to the  $\alpha$ 4-integrin (VLA-4) that inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Furthermore, the antibodies to VLA-4 inhibited the induced IL-6 secretion. Furthermore, Lokhorst *et al* teach that the intimate cell-cell contact is a prerequisite for IL-6 induction and the physical separation of plasma cells and LTBMC by mechanical means such as monoclonal antibodies to VLA-4 which is involved in the adhesion process, inhibit the induction of IL-6 production by LTBMC. (entire document and abstract page 2269, and page 2276, left column 2<sup>nd</sup> paragraph in particular).

The '786 patent teaches that melphalan is available in tablet form for oral administration and has been used to treat multiple myeloma. Further, the '786 patent teaches that available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug (see col., 29 under Melphalan in particular).

Alexanian *et al* teach a method of treating multiple myeloma using a combination therapy with melphalan and prednisone melphalan with a higher response rate in comparison with melphalan alone (see abstract in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody taught by the Van Zaanen *et al* with the antibody that specifically binds the  $\alpha$ 4 integrin taught by Masellis-Smith *et al* or Lokhorst *et al.*, and combined the anti- $\alpha$ 4 antibody with melphalan as taught by the '786 patent or Alexanian *et al* in a method of treating multiple myeloma (MM).

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the anti-IL-6 antibodies with anti- $\alpha$ 4 antibodies in a method of treating MM because antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst *et al* and because antibodies against alpha4 integrin inhibit the adhesion of alpha4beta7 integrin of B cells from MM patients with its ligand on the bone marrow (BM) fibroblast and hence prevent extravasation into the BM. Further, melphalan is currently used in the treatment of multiple myeloma and available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug as taught by the '786 patent. In addition, the combination therapy with melphalan provides a higher response rate in comparison with melphalan alone as taught by Alexanian *et al* reference. Moreover, the motivation to combine the anti- $\alpha$ 4 antibody with melphalan can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose (i.e., treating MM). Section MPEP 2144.07. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Claims 93-95 are included because the determination of the optimal dosage of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. Further, it has been held that where the

Art Unit: 1644

general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP §§ 2144.05 part II A.

Claim 97 is included because the referenced anti-VLA-4 antibodies are functionally blocking antibodies.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claim 92 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. A1 and Lokhorst et al (Blood 84:2269-2277, 1994) and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969). as applied to claims 86-89, 91, 93-97 and 101 above, and further in view of Owens et al (1994).

The teachings of Van Zaanen et al, Masellis-Smith et al, Lokhorst et al, the '786 patent and Alexanian et al reference have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a chimeric antibody, a Fab fragment, a F(ab')<sub>2</sub> fragment or a humanized antibody in claim 92.

Owens et al teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')<sub>2</sub> fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and F(ab')<sub>2</sub>. Owens et al further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxicity (see the entire document).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Masellis-Smith et al or Lokhorst et al as chimeric, humanized antibody, Fab and F(ab')<sub>2</sub> fragments taught by the Owens et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxicity as taught by Owens et al.

Art Unit: 1644

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claim 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. A1 and Lokhorst et al (Blood 84:2269-2277, 1994) and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969). as applied to claims 86-89, 91, 93-97 and 101 above, and further in view of U.S. Pat. No. 5,840,299.

The teachings of Van Zaanen et al, Masellis-Smith *et al*, Lokhorst *et al*, the '786 patent and Alexanian *et al* reference have been discussed, *supra*.

The claimed invention differs from the reference teaching only by the recitation of an anti-VLA-4 homolog comprising a humanized light chain and a humanized heavy chain, the light chain and the heavy chain each comprising CDRs (CDR1, CDR2 and CDR3) from a murine 21.6 anti-VLA antibody in claims 99 and 100, wherein (a) the humanized light chain comprises a variable region framework from a human kappa light chain variable region framework sequence, wherein at least one amino acid position of the framework region is occupied by the amino acid present in the equivalent position of the murine 21.6 immunoglobulin light chain variable region framework, and (a) the humanized heavy chain comprises a variable region framework from a human heavy chain variable region framework region is occupied by the amino acid present in the equivalent position of the murine 21.6 immunoglobulin heavy chain variable region framework in claim 99.

The '299 patent teaches the construction of Reshaped Human 21.6 antibodies. The first version of reshaped human 21.6 VL region which is constructed from overlapping PCR fragments (see table 6, col. 22-23 in particular). The second version of a reshaped human 21.6 VL region is constructed using PCR primers to make minor modifications in the first version of reshaped human 21.6 VL (see col. 23, lines 62-67 in particular). Further, the '299 patent teaches reshaped human 21.6 VH region is constructed using same PCR methods (see col., 24, lines 55-67 in particular). The '299 patent teaches that the animal experiments test the effect of anti-VLA-4 antibodies on animals having an artificially induced condition, simulating multiple sclerosis, wherein the experiments show that administration of anti-VLA-4 antibodies prevents inflammation of brain and subsequent paralysis in the animals ( see col., 1 line 66 through col. 2, line 8 in particular). The '299 patent teaches that humanized anti-VLA-4 antibodies demonstrate strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response (see col. 2, lines 43-47 in particular). Finally, the '299 patent teaches that the humanized light and heavy chain variable region frameworks are from RE1 and 21/28'CL variable region framework sequences respectively. When the humanized light chain variable region framework is from RE1, at least two framework amino acids are replaced. One amino acid is from the first

Art Unit: 1644

group of positions described supra. The other amino acids is from a third group consisting of positions L104, L105 and L107. This position is occupied by the same amino acid present in the equivalent position of a kappa light chain from a human immunoglobulin other than RE1 (col., 3, lines 13-23 in particular).

Given that humanized anti-VLA-4 antibodies demonstrate strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody taught by the Van Zaanen *et al* with the antibody homolog comprising a humanized antibody 21.6 taught by the '299 patent, and combined the anti- $\alpha$ 4 antibody with melphalan as taught by the '786 patent or Alexanian *et al* in a method of treating multiple myeloma (MM).

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because humanized anti-VLA-4 antibodies demonstrate strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response. Further, melphalan is currently used in the treatment of multiple myeloma and available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug as taught by the '786 patent. In addition, the combination therapy with melphalan provides a higher response rate in comparison with melphalan alone as taught by Alexanian *et al* reference. Moreover, the motivation to combine the anti- $\alpha$ 4 antibody with melphalan can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose (i.e., treating MM). Section MPEP 2144.07. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 86-89, 91, 93-97 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,495,525 in view of Kamata *et al* and U.S. Patent No. 5,885,786 or Alexanian *et al* (JAM, 208:1680-1685, 1969).

The '525 patent teaches a method for treating multiple myeloma in a mammal comprising administering to a compounds which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V (see patented claim 9, col., 30, and col., 4, line 21-40 in particular). The '525 patent further teaches anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo (see col., lines 57-58 in particular). Additionally, the '525 patent teaches that the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of

Art Unit: 1644

VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin. These compounds are useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. These compounds are useful for inhibition, prevention and suppression of VLA-4-mediated cell adhesion and pathologies associated with that adhesion such as multiple myeloma (col., 2, line 64 through col., 3, line 21 in particular). Finally, the '525 patent teaches the composition is employed in dosage range from about 0.001-25 mg/kg (see col., 10, lines 60-63 in particular).

The claimed invention differs from the reference teachings only by the recitation of a combination of an anti-VLA-4 antibody and a chemotherapeutic agent in claims 85 and 101, wherein the chemotherapeutic agent is melphalan in claim 88, wherein the antibody is a monoclonal antibody in claim 91, a dosage that is lower when administered in combination with said second composition in claims 93-95, wherein the anti-VLA-4 antibody binds the alpha chain of VLA-4 in claim 96, wherein the anti-VLA-4 antibody is a B epitope specific anti-VLA-4 antibody in claim 97.

Kamata et al teach that the anti-alpha 4 functional blocking antibodies such as P4C2 (epitope B2) and P4G9 (within residues 1-52) (see abstract in particular).

The '786 patent teaches that melphalan is available in tablet form for oral administration and has been used to treat multiple myeloma. Further, the '786 patent teaches that available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug (see col., 29 under Melphalan in particular).

Alexanian et al teach a method of treating multiple myeloma using a combination therapy with melphalan and prednisone melphalan with a higher response rate in comparison with melphalan alone (see abstract in particular).

Claims 93-95 are included because the determination of the optimal dosage of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454, 456, 105 USPQ 233; 235 (CCPA 1955). see MPEP §§ 2144.05 part II A.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the compound which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V taught by the '525 patent with anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4-dependent adhesion interactions both in vitro and in vivo taught by the '525 patent in a method for treating MM as taught by the '525 patent or substitute the anti-VLA-4 monoclonal antibody taught by the '525 patent Kamata et al and combined the anti- $\alpha$ 4 antibody with melphalan as taught by the '786 patent or Alexanian *et al* in a method of treating multiple myeloma (MM).

Art Unit: 1644

Given that the anti- $\alpha$ -4 antibodies are functional blocking antibodies that binds to B2 epitope and that the combination therapy of MM leads to a higher response rate, one of ordinary skill in the art at the time the invention was made would have been motivated to do so because the '525 suggested the substitution implicitly because the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin such is antibodies to VLA-4. These compounds are useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. Further, the Kamata's et al antibodies are functional blocking. Further, melphalan is currently used in the treatment of multiple myeloma and available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug as taught by the '786 patent. Moreover, the motivation to combine the anti- $\alpha$ 4 antibody with melphalan can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose (i.e., treating MM). Section MPEP 2144.07. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claim 92 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,495,525 in view of Kamata et al and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969) as applied to claims 86-89, 91, 93-97 and 101 above, and further in view of Owens *et al* (1994).

The teachings of the '525 patent, Kamata *et al*, the '786 patent and Alexanian *et al* reference have been discussed, *supra*.

The claimed invention differs from the reference teaching only by the recitation of a chimeric antibody, a Fab fragment, a F(ab')<sub>2</sub> fragment or a humanized antibody in claim 92.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')<sub>2</sub> fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and F(ab')<sub>2</sub>. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxicity (see the entire document).



Art Unit: 1644

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Kamata *et al* as chimeric, humanized antibody, Fab and F(ab')<sub>2</sub> fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxicity as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claim 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,495,525 in view of Kamata *et al* and U.S. Patent No. 5,885,786 or Alexanian *et al* (JAM, 208:1680-1685, 1969) as applied to claims 86-89, 91, 93-97 and 101 above, and further in view of U.S. Pat. No. 5,840,299.

The teachings of the '525 patent, Kamata *et al*, the '786 patent and Alexanian *et al* reference have been discussed, *supra*.

The claimed invention differs from the reference teaching only by the recitation of an anti-VLA-4 homolog comprising a humanized light chain and a humanized heavy chain, the light chain and the heavy chain each comprising CDRs (CDR1, CDR2 and CDR3) from a murine 21.6 anti-VLA antibody in claims 99 and 100, wherein (a) the humanized light chain comprises a variable region framework from a human kappa light chain variable region framework sequence, wherein at least one amino acid position of the framework region is occupied by the amino acid present in the equivalent position of the murine 21.6 immunoglobulin light chain variable region framework, and (a) the humanized heavy chain comprises a variable region framework from a human heavy chain variable region framework region is occupied by the amino acid present in the equivalent position of the murine 21.6 immunoglobulin heavy chain variable region framework in claim 99, .

The '299 patent teaches the construction of Reshaped Human 21.6 antibodies. The first version of reshaped human 21.6 VL region which is constructed from overlapping PCR fragments (see table 6, col. 22-23 in particular). The second version of a reshaped human 21.6 VL region is constructed using PCR primers to make minor modifications in the first version of reshaped human 21.6 VL (see col. 23, lines 62-67 in particular). Further, the '299 patent teaches reshaped human 21.6 VH region is constructed using same PCR methods (see col., 24, lines 55-67 in particular). The '299 patent teaches that the animal experiments test the effect of anti-VLA-4

Art Unit: 1644

antibodies on animals having an artificially induced condition, simulating multiple sclerosis, wherein the experiments show that administration of anti-VLA-4 antibodies prevents inflammation of brain and subsequent paralysis in the animals ( see col., 1 line 66 through col. 2, line 8 in particular). The '299 patent teaches that humanized anti-VLA-4 antibodies demonstrate strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response (see col. 2, lines 43-47 in particular). Finally, the '299 patent teaches that the humanized light and heavy chain variable region frameworks are from RE1 and 21/28'CL variable region framework sequences respectively. When the humanized light chain variable region framework is from RE1, at least two framework amino acids are replaced. One amino acid is from the first group of positions described supra. The other amino acid is from a third group consisting of positions L104, L105 and L107. This position is occupied by the same amino acid present in the equivalent position of a kappa light chain from a human immunoglobulin other than RE1 (col., 3, lines 13-23 in particular).

Given that humanized anti-VLA-4 antibodies demonstrate strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the compound which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V taught by the '525 patent with anti-VLA-4 homolog antibody comprising a humanized 21.6 murine 21.6 anti-VLA-4 antibody as taught by the '299 patent and combined the anti- $\alpha$ 4 antibody with melphalan as taught by the '786 patent or Alexanian *et al* in a method of treating multiple myeloma (MM).

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because humanized anti-VLA-4 antibodies demonstrate strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response. Further, melphalan is currently used in the treatment of multiple myeloma and available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug as taught by the '786 patent. In addition, the combination therapy with melphalan provides a higher response rate in comparison with melphalan alone as taught by Alexanian *et al* reference. Moreover, the motivation to combine the anti- $\alpha$ 4 antibody with melphalan can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose (i.e., treating MM). Section MPEP 2144.07. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Art Unit: 1644

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 86-89, 91, 93-96 and 101 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-16 of copending Application No. 09/943,659. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 12-16 of Application '659 are drawn to the same method of treatment using a composition comprising an antagonist of an interaction between an  $\alpha 4$  subunit-bearing integrin and a ligand for an  $\alpha 4$  subunit-bearing integrin in combination of melphalan as a chemotherapeutic agent. While the instant applicant claiming a method for treating MM comprising with anti-VLA-4 antibody in combination with melphalan.

Claim 91 is included because the antagonist of an interaction between an  $\alpha 4$  subunit-bearing integrin and a ligand for  $\alpha 4$  subunit-bearing integrin can be anti-VLA-4 antibodies, including monoclonal antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claim 92 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-16 of copending Application No. 09/943,659 in view of Owens et al

The teachings of claims 12-16 of Application '659, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a chimeric antibody, a Fab fragment, a F(ab')<sub>2</sub> fragment or a humanized antibody in claim 92.

Art Unit: 1644

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')<sub>2</sub> fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and F(ab')<sub>2</sub>. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxicity (see the entire document).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce the anti-alpha-4 antibody taught by the claims of '659 application as chimeric, humanized antibody, Fab and F(ab')<sub>2</sub> fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxicity as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claim 97 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-16 of copending Application No. 09/943,659 in view of Kamata *et al*.

The teachings of claims 12-16 of Application '659 and Kamata *et al*., have been discussed, *supra*.

The claimed invention differs from the reference teachings only by the recitation of a B epitope.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody against VLA-4 taught by the '659 application with anti-alpha 4 functional blocking antibodies such as P4C2 (epitope B2) taught by Kamata *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the Kamata's *et al* antibodies are functional blocking antibodies.

Art Unit: 1644

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claims 98-100 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-16 of copending Application No. 09/943,659 in view of U.S. Pat. No. 5,840,299.

The teachings of claims 12-16 of Application '659 and the '299 patent., have been discussed, *supra*.

The claimed invention differs from the reference teachings only by the recitation of an anti-VLA-4 homolog comprising a humanized light chain and a humanized heavy chain, the light chain and the heavy chain each comprising CDRs (CDR1, CDR2 and CDR3) from a murine 21.6 anti-VLA antibody in claims 99 and 100, wherein (a) the humanized light chain comprises a variable region framework from a human kappa light chain variable region framework sequence, wherein at least one amino acid position of the framework region is occupied by the amino acid present in the equivalent position of the murine 21.6 immunoglobulin light chain variable region framework, and (a) the humanized heavy chain comprises a variable region framework from a human heavy chain variable region framework region is occupied by the amino acid present in the equivalent position of the murine 21.6 immunoglobulin heavy chain variable region framework in claim 99 ..

Given that humanized anti-VLA-4 antibodies demonstrate strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody against alpha-4 taught by the '659 application with the antibody homolog comprising a humanized antibody 21.6 taught by the '299 patent in a method of treating multiple myeloma (MM).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection.

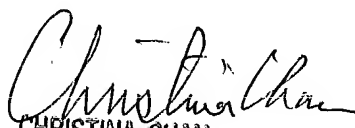
Art Unit: 1644

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.  
Patent Examiner  
Technology Center 1600  
October 27, 2004

  
CHRISTINA CHAN  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600